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Fulminant Type 1 Diabetes Mellitus in IRS-2 Deficient Mice

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1. Introduction

Type 1 diabetes mellitus (T1DM), one of two major forms of diabetes, results from nearly complete destruction of pancreatic beta (β) cells. According to the classification of diabetes made by the American Diabetes Association, T1DM is divided into two subtypes: immune-mediated (type 1A) and idiopathic (type 1B) (American Diabetes Association, 2008). Fulminant type 1 diabetes mellitus (FT1DM), which was first reported by Imagawa et al. in 2000, is thought to be a unique subtype of type 1B diabetes. The initial reports of FT1DM were exclusively in Japanese population and accounted for about 20% of their T1DM (Imagawa et al., 2000; 2003). Outside Japan, Cho et al. (2007) reported prevalence for FT1DM of 7.1% in the newly diagnosed Korean T1DM patients. However, epidemiological study of FT1DM is lacking in other Asian populations and its incidence and pathogenesis remain to be elucidated. While a search for FT1DM was reported to be negative in the Caucasian population, case reports on FT1DM had surfaced in different ethnic groups, predominantly from Asian origins (Jung et al., 2004; Taniyama et al., 2004; Moreau et al., 2008). However, the causative mechanism of FT1DM is currently unknown. On the other hand, insulin receptor substrate (IRS) disorders are associated with onset of insulin resistance and diabetes mellitus (Withers et al., 1998; Kido et al., 2000). A small population of male IRS-2 deficient mice showed hyperglycemia associated with markedly diminished pancreatic islet size, and these extremely hyperglycemic IRS-2 deficient mice exhibited 1) abrupt onset of diabetes and 2) very short duration of diabetic symptoms, such as polyuria, thirst, and body weight loss. These symptoms resembled the features of human nonautoimmune FT1DM (Hashimoto et al., 2006). Characteristics of abrupt onset of hyperglycemia associated with marked diminished islet mass in IRS-2 deficient mice were investigated to analyze the onset mechanism of FT1DM.

2. Characteristics of fulminant type 1 diabetes mellitus

2.1 Onset of fulminant type 1 diabetes mellitus

Fulminant type 1 diabetes mellitus (FT1DM) is a novel clinical entirely within diabetes mellitus and accounts for 20% of T1DM in Japan. Since its initial description by Imagawa et al. (2000), many cases have been reported predominately in Japan and Korea. FT1DM shows clinical characteristics of (1) remarkably abrupt onset of disease; (2) very short (< 1 week) duration of diabetic symptoms, such as polyuria, thirst and body weight loss; (3) acidosis at

diagnosis; (4) negative status of islet-related antibodies, islet cell antibodies (ICA), anti-glutamic acid decarboxylase antibodies (GADAb), insulin autoantibodies (IAA) or anti-islet antigen 2 antibodies (IA-2); (5) virtually no C-peptide secretion (< 10 μg/day in urine); and (6) elevated serum pancreatic enzyme level. Fas and Fas ligand expression are lacking and the mechanism of β cell destruction differs from that in autoimmune T1DM. However the degradation mechanism of β cell in FT1DM of humans is unknown. Recently, it has been reported that the onset of FT1DM may be attributed to certain HLA subtype, to viral infection, or to pregnancy (Imagawa et al., 2003; Imagawa et al., 2005; Shimizu et al., 2006; Kawabata et al., 2009). In recent study, macrophages and T cells - but not natural killer cells – had infiltrated the islets and the exocrine pancreas and Toll-like receptor (TLR) 3, a sensor of viral components, was detected in most of macrophages and T cells in FT1DM patients (Shibasaki et al., 2010). Their study showed remarkably decreased numbers of pancreatic beta and alpha cells, macrophage-dominated insulitis and the expression of TLRs, a signature of viral infection, in FT1DM soon after the disease onset. These results suggest a new mechanism of virus-induced macrophage-dominated inflammatory process, rather than autoimmune T cell response, plays a major role in β cell destruction in FT1DM.

2.2 FT1DM associated with viral infection

Causative mechanism for accelerated β cell destruction in FT1DM is unclear. To date, viral infection has been the most popular speculated cause of acute destruction of the pancreatic β cell as many patients reported flu-like symptoms prior to the disease onset (Zheng et al., 2011). Tanaka et al (2009) investigated islet cell status, including the presence of enterovirus and chemokine/cytokline/major histocompatibility complex (MHC) expression in the pancreata using immunohistochemical analyses in three subjects with FT1DM. Immunohistochemical analyses revealed the presence of enterovirus-capsid protein in all three affected pancreata. Extensive infiltration of CXCR3 receptor-bearing T-cells and macrophages into islets was observed. Dendritic cells were stained in and around the islets. Interferon-γ and CXC chemokine ligand 10 (CXCL10) were strongly coexpressed in all subtypes of islet cells, including β cell and α cells. No CXCL10 was expressed in exocrine pancreas. Serum levels of CXCL10 were increased. Expression of MHC class II and hyper-expression of MHC class I was observed in some islet cells. These observations strongly suggest the presence of a circuit for destruction of β cells in FT1DM. Enterovirus infection of the pancreata initiates coexpression of interferon-γ and CXCL10 in β cells. CXCL10 secreted from β cells activates and attracts autoreactive T-cells and macrophages to the islets via CXCR3. These infiltrating autoreactive T-cells and macrophages release inflammatory cytokines including interferon-γ in the islets, not only damaging β cells but also accelerating CXCL10 generation in residual β cells and thus further activating cell-mediated autoimmunity until all β cells have been destroyed. On the other hand, Shibasaki et al (2010) investigated pathogenesis of FT1DM with special reference to insulitis and viral infection using pancreatic autopsy samples from three patients. Both β and α cell area were significantly decreased in comparison with those of normal controls. Macrophages and T cells – but not natural killer cells – had infiltrated the islets and the exocrine pancreas. Toll-like receptor (TLR) 3, a sensor of viral components, was detected in 84.7% of macrophages and 62.7% of T cells in all three patients. TLR7 and TLR9 were also detected in the pancreas of all three patients. Enterovirus RNA was detected in β cells positive islets in one of the three patients by *in situ* hybridization. These results suggest that macrophage-dominated

inflammatory process, rather than autoimmune T cell response, plays a major role in β cell destruction in FT1DM.

2.3 FT1DM associated with pregnancy

FT1DM associated with pregnancy is very rare. However if it occurs, the rapid onset is associated with an extremely high risk of fetal death. Therefore, it is important for physicians to make an appropriate diagnosis as early as possible and to begin immediate treatment of both the mother and the fetus (Murabayashi et al., 2009). Shimizu et al. (2006) characterized the clinical and immunogenetic features of Japanese pregnancy-associated FT1DM (PF). A group of patients with PF was compared with a group of patients of child-bearing age with FT1DM that was not associated with pregnancy (NPF) in a nationwide survey conducted from 2000-2004. The criteria used for inclusion of FT1DM were 1) ketosis or ketoacidosis within 1 week after the onset of hyperglycemic symptoms; 2) urinary C peptide excretion less than 10 μg/day, fasting serum C peptide levels less than 0.3ng/ml, or serum C peptide levels less than 0.5 ng/ml after glucagon injection or a meal load soon after the onset of the disease; and 3) hemoglobin A_{1c} levels less than 8.5% on the first visit. Twenty two PF patients showed increased plasma amylase values and negative for GADab except one with transient increase in GADab (12U/ml). In 22 PF patients, 18 developed disease during pregnancy, whereas four cases occurred immediately after delivery. Twelve cases that developed during pregnancy resulted in stillbirty, and five of the six fetal cases that survived were delivered by cesarean section. The haplotype frequency of HLA DRB1*0901-DQB1*0303 in PF was significantly higher than those in NPF and controls, whereas that of DRB1*0405-DQB1*0401 in NPF was significantly higher than those in PF. The type 1 diabetes-susceptible HLA class II haplotype is distinct in PF and NPF patients, suggesting that different HLA haplotypes underlie the presentation of PF or NPF. Moreau et al. (2008) reported three cases of FT1DM in Caucasian French women. HLA phenotyping of these Caucasian patients did not find the specific HLA haplotype (DRB1*0405-DQB1*0401) found to be linked to FT1DM in Japanese patients. Two cases of FT1DM associated with pregnancy was reported from Malaysia (Tan & Loh, 2010), and FT1DM as subtype of type1B diabetes with severe and persistent β cell failure may be an important subtype in the young adult Asian populations. More international collaborative epidemiological studies are warranted in order to better understand and characterize FT1DM associated with pregnancy.

3. Metabolic disorders in IRS-2 deficient mice

3.1 IRS-2 deficient mouse

Insulin receptor substrate (IRS) disorders are associated with onset of insulin resistance and diabetes mellitus. IRS-1 deficient mice are growth-retarded and show skeletal muscle insulin resistance but do not develop diabetes because the hyperinsulinemia associated with the β cell hyperplasia in these mice efficiently compensates for the insulin resistance (Withers et al., 1998; Kido et al., 2000). IRS-2 deficient mice develop diabetes, presumably due to inadequate β cell proliferation combined with insulin resistance, and the insulin resistance in IRS-2 deficient mice is ameliorated by reduction of adiposity. IRS-2 deficient mice are widely used for analysis of pathophysiology of human type 2 diabetes mellitus (T2DM). In

male IRS-2 deficient mice (C57BL/6 x CBA hybrid background) generated by Kubota et al. (2000) with C57BL/6J:Jcl mice established an inbred line of IRS-2 deficient mice, serious T1DM accompanied by abrupt and marked increase of their plasma glucose concentrations and ketonuria was sometimes observed (Hashimoto et al., 2006). The symptoms observed in IRS-2 deficient mice with serious T1DM with insulin-deficient hyperglycemia resembled those of human nonautoimmune FT1DM reported by Imagawa et al. (2000). Analyses of plasma metabolite, insulin, C-peptide, hepatic enzyme activities related to energy metabolism and histopathological changes in pancreas and islet-related antibodies may clarify the mechanism of β cell destruction and onset of FT1DM in animals.

3.2 Metabolic characteristics in IRS-2 deficient mice

We established an inbred line of mice deficient in insulin receptor substrate-2 (IRS-2) that have a C57BL/6J genetic background (B6J-IRS2$^{-/-}$ mice). At 6 week of age, there was no difference in body weight between wild-type (control) and IRS-2 deficient mice, but IRS-2 deficient mice showed remarkable impaired glucose tolerance and insulin resistance (Hashimoto et al., 2006). IRS-2 deficient mice showed significant increases in plasma glucose, free fatty acid (FFA), triglyceride (TG), total cholesterol (TC) and insulin concentrations compared to wild-type (control) mice at 6-week-old. In the livers of male IRS-2 deficient mice, the activities of cytosolic pyruvate kinase (PK), glucose-6-phosphate dehydrogenase (G6PD), ATP citrate lyase (ACL), fatty acid synthase (FAS) and malic enzyme (ME) were significantly higher than those of control mice (Table 1). Increase in activities of G6PD, ACL, FAS and ME, which are crucial enzymes for fatty acid synthesis, means activation of lipid synthesis in liver of IRS-2 deficient mice. Insulin resistance observed in IRS-2 deficient mice tends to deteriorate with aging. On the other hand, two of eight male IRS-2 deficient mice each at the ages of 14 and 24 week suddenly showed extreme hyperglycemia, similar to that in case of FT1DM. Another 2 male IRS-2 deficient mice developed extreme hyperglycemia at the age of 11 and 12 week and died. Plasma glucose and FFA concentrations in the extremely hyperglycemic IRS-2 deficient mice showed abnormal increases compared with moderately hyperglycemic IRS-2 deficient mice. Plasma insulin concentrations in extremely hyperglycemic IRS-2 deficient mice were below the detection limit. On histopathologic examination, the pancreatic islets of extremely hyperglycemic IRS-2 deficient mice were either absent or decreased in size and number compared with those of moderately hyperglycemic IRS-2 deficient mice. The islets of extremely hyperglycemic IRS-2 deficient mice showed karyorrhexis, cytoplasmic swelling, and partial necrosis. In addition, the liver of one extremely hyperglycemic IRS-2 deficient mouse showed collagen fibrinoid degeneration and macrophages.

In conclusion, at 6 week of age, IRS-2 deficient mice showed profiles compatible with several features of metabolic syndrome, including hyperglycemia, hyperinsulinemia, insulin resistance, hypertriglyceridemia, and high FFA concentrations. Therefore even young IRS-2 deficient mice are useful animal models for studying T2DM. Moreover, hyperglycemia and insulin resistance in these mice progressed to their highest levels when the animals were 14 week of age. A small population of male IRS-2 deficient mice developed abrupt onset of hyperglycemia associated with markedly diminished islet mass, resembling the features of human nonautoimmune FT1DM. The IRS-2 deficient mice may also serve as an animal model for studying FT1DM.

			Wild-type (n=8)	IRS-2 deficient (n=8)
Plasma	Glucose (mg/dl)		152 (8)	223 (23)*
	Free fatty acid (mEq/l)		0.26 (0.03)	0.49 (0.09)*
	Triglyceride (mg/dl)		55.4 (2.5)	75.8 (8.4)*
	Total cholesterol (mg/dl)		54.8 (2.6)	88.0 (8.1)*
	Insulin (ng/ml)		0.74 (0.10)	2.01 (0.35)*
Liver	Cytosol	HK	5.6 (0.3)	6.0 (0.6)
		GK	1.4 (0.1)	1.6 (0.2)
		PK	11.1 (1.5)	14.8 (1.4)*
		G6PD	6.0 (0.7)	8.5 (0.8)*
		LDH	1658 (75)	1633 (83)
		MDH	4340 (211)	4342 (162)
		AST	546 (60)	577 (57)
		ACL	4.4 (0.4)	5.9 (0.4)*
		FAS	7.7 (0.6)	10.8 (1.1)*
		ME	10.1 (1.2)	20.1 (2.0)*
		PEPCK	20.9 (2.2)	22.3 (2.8)
	Microsomes	G6Pase	424 (11)	440 (22)
	Mitochondria	GLDH	1264 (96)	1462 (78)
		MDH	3985 (216)	4247 (349)
		AST	1008 (110)	981 (55)

Data are presented as mean (SE).
*P<0.05 (Student's *t* test) versus value for wild-type mice.
Hepatic enzyme activities are presented as nmol/min/mg protein.
HK, hexokinase; GK, glucokinase; PK, pyruvate kinase; G6PD, glucose-6-phosphate dehydrogenase; LDH, lactate dehydrogenase; MDH, malate dehydrogenase; AST, aspartate aminotransferase; ACL, ATP citrate lyase; FAS, fatty acid synthase; ME, malic enzyme; PEPCK, phosphoenolpyruvate carboxykinase; G6Pase, glucose-6-phosphatase; GLDH, glutamate dehydrogenase

Table 1. Plasma metabolite concentrations and hepatic enzyme activities in 6-week-old male wild-type and IRS-2 deficient mice

3.3 Obesity with insulin resistance in IRS-2 deficient mice with high-fat diet feeding

Type 2 diabetes mellitus (T2DM) appears to be increasing mainly in the United States, Africa and Asia. In 2000 there were one hundred and fifty million T2DM patients, but they are predicted to increase substantially to two hundred and twenty million world-wide in 2010. Since World War II (WWII), T2DM patients have increased markedly with dramatic changes of lifestyle in Japan. Typical changes of the lifestyle include the increases in high fat diets, sedentary habit and driving. Especially, the level of fat in modern Japanese diets increased from 20.0 g/day in 1953 to 59.9 g/day in 1995 according to the nation-wide nutrition monitoring survey in Japan. Japanese population is predisposed to develop T2DM due to insufficient insulin secretion in spite of no predisposition to obesity. IRS-2 deficient mice show at 6 weeks of age showed profiles compatible with several features of the metabolic syndrome, including hyperglycemia, hyperinsulinemia, insulin resistance, hypertriglyceridemia, and high FFA. To investigate the characteristics in energy metabolism in IRS-2 deficient, three kinds of diets with different lipid concentrations were supplied to IRS-2 deficient mice (4 weeks old) for 2weeks. Total calories of diets were calculated as 395.1

kcal/100g for Modern American diet, 365.0 kcal/100g for Modern Japanese diet and 328.9 kcal/100g for Japanese diet after WWII. Each diet contained 15.5% (American diet, Ad), 10.1% (Japanese diet, Jd) and 3.9% (WWII diet) as crude fat, respectively. Regular diet (Rd) for laboratory animals (390kcal/100g) contained 5.0% as crude fat were based on human Japanese diet after WWII. Male IRS-2 deficient mice (4 weeks old) were provided with

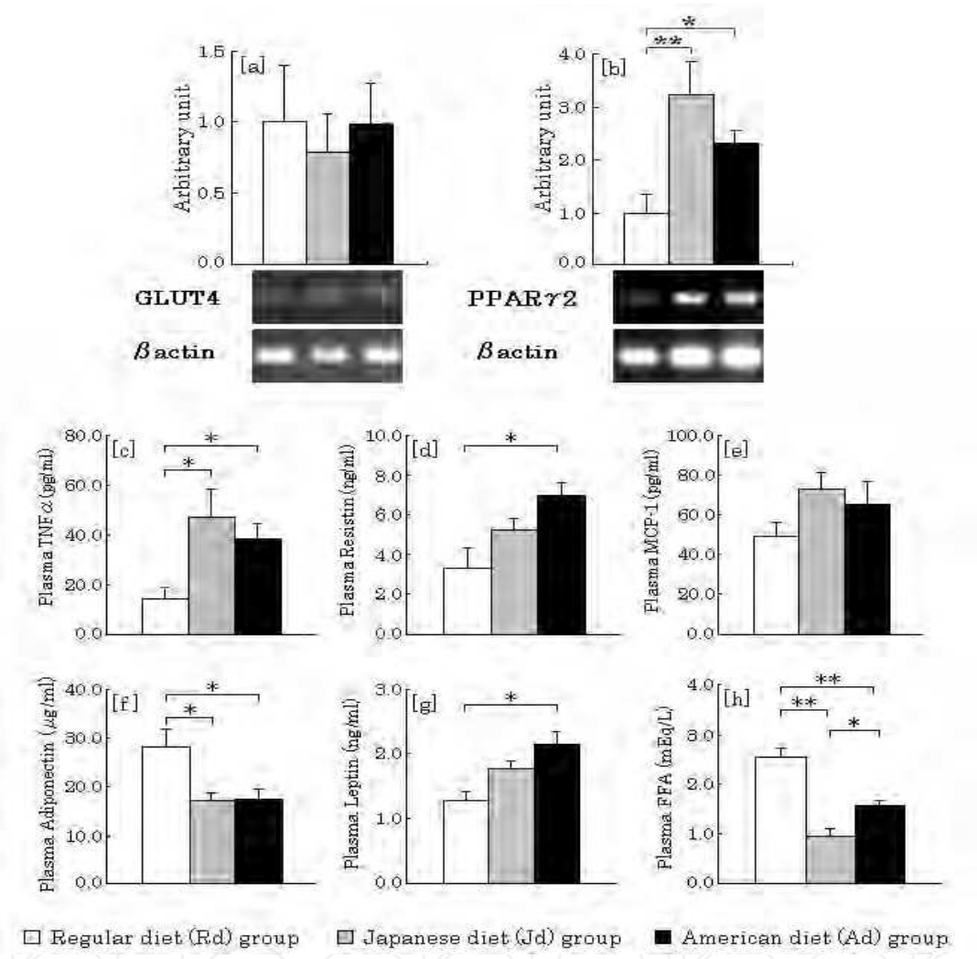


Fig. 1. Effects of modern Japanese and American diets on RNA expression of GLUT4 and PPARγ2 of adipose tissues and plasma adipocytokines concentrations in IRS-2 deficient mice fed with three kinds of diets with different lipid levels.

regular and Japanese and American diets as well as tap water *ad libitum* for 2 weeks, and used for glucose tolerance test, insulin tolerance test, and harvests of blood, liver, femoral muscles, white adipose tissue (WAT), and pancreas for chemical analysis at the age of 6 weeks (Hashimoto et al., 2009). Average body weight of Rd, Jd and Ad group at 6 week of age were 20.8, 22.7 and 22.9g each. Japanese and American diet increased significantly the body weight of IRS-2 deficient mice when compared with regular diet. Ad group showed severely impaired glucose tolerance, and Jd and Ad group showed deterioration of insulin resistance. Expression of SREBP-1c mRNA in the livers of Ad group was increased with Rd group ($p<0.05$). In addition, expression of PPARγ2 mRNA and GLUT2 mRNA in the Ad group were higher than in other groups ($p<0.05$). Cytosolic ACL and ME activities in the

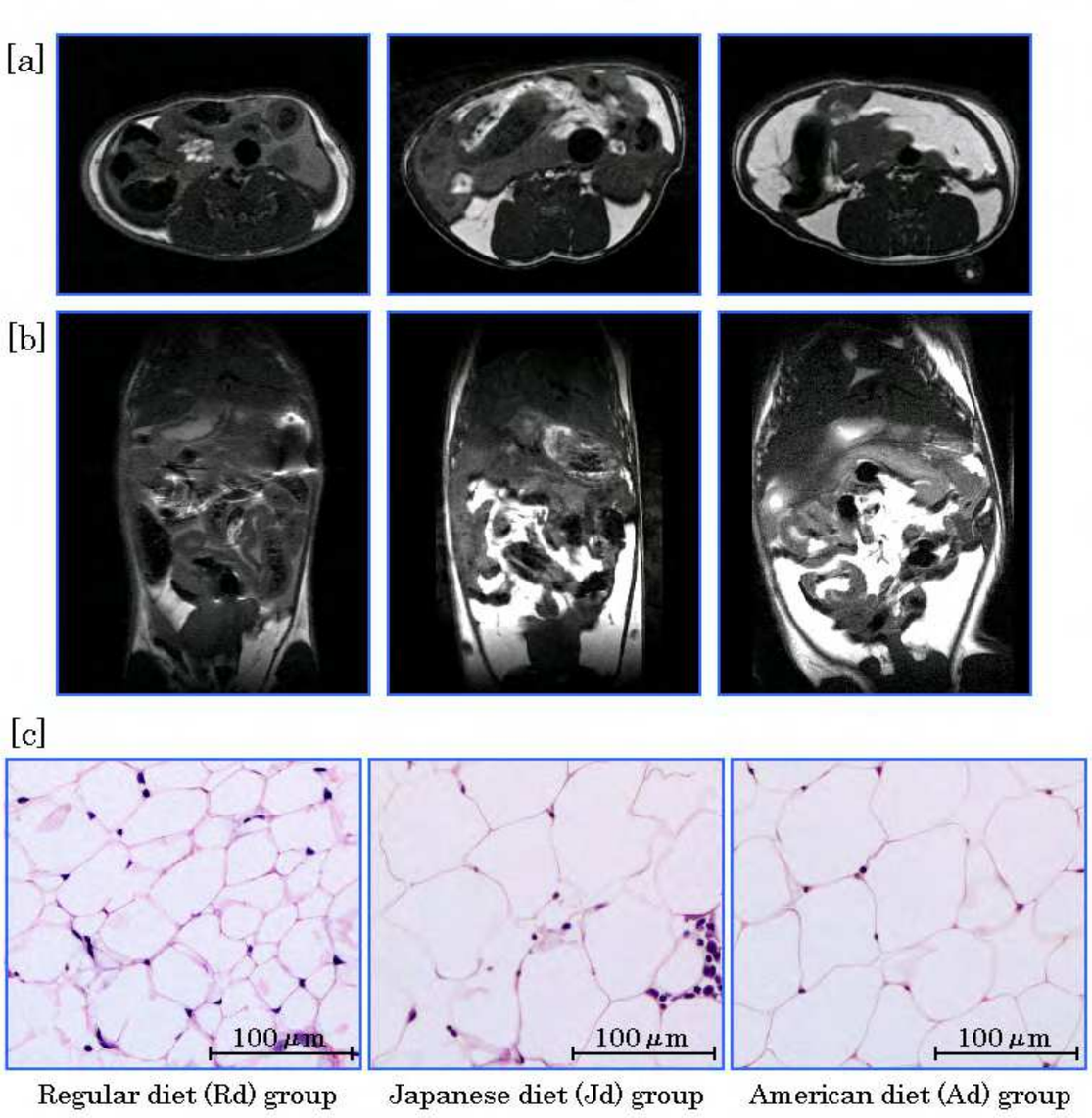


Fig. 2. Effects of modern Japanese and American diets on intraperitoneal white adipose tissues, (a) Axial views, (b) Coronal views of MRI, and (c) Adipocytes in white adipose tissues of IRS-2 deficient mice with three kinds of diets with different lipid levels.

livers of the Jd and Ad groups increased when compared with the Rd group ($p<0.05$). Expression of GLUT4 mRNA in the skeletal muscle of the Jd and Ad groups were lower than that in the Rd group ($p<0.01$). Figure 1 shows expression of mRNA in WAT and plasma cytokine concentrations in IRS-2 deficient mice. Expression of GLUT4 mRNA was not changed in WAT of each group. Expression of PPARγ2 mRNA in the Jd and Ad groups was higher than that in the Rd group ($p<0.05$). Both the Jd and Ad groups showed increased plasma TNF-α concentrations compared with the Rd group ($p<0.05$). In addition, the Ad group showed increased plasma resistin concentrations compared with other groups ($p<0.05$). However, plasma MCP-1 concentrations were not altered. On the other hand, both

of Jd and Ad groups showed decreased plasma adiponectin concentrations compared with the Rd group ($p<0.05$). The Ad group showed increased plasma leptin concentrations compared with the Rd group ($p<0.05$). Both the Jd and Ad groups showed decreased plasma FFA concentrations compared with the Rd group ($p<0.05$). MRI showed the effects of Japanese and American diets on intraperitoneal WAT in IRS-2 deficient mice. Peritoneal WAT was accumulated in mice fed on Japanese and American diets. WAT around the kidney and testes in the Jd and Ad groups increased in proportion to fat concentrations of diets when compared with the Rd group. In addition, adipocytes of the Jd and Ad groups were corpulent when compared with those of the Rd group (Figure 2c). Expression of GLUT2 mRNA in pancreas of the Ad group was the lowest among all groups ($p<0.05$). The Jd and Ad groups showed hyperinsulinemia when compared with Rd group ($p<0.05$). On histopathologic examination of islets, insulin secretion was observed in all three groups.

In conclusion, high-fat diet feeding induced rapid accumulation of fat intraperitoneal cavity of IRS-2 deficient mice. Obese IRS-2 deficient mice showed higher activities of lipid synthesis in their livers and the increase in TNF-α of corpulent adipocyte origin further aggravated insulin resistance and the increase in resistin also aggravated the impaired glucose tolerance, leading to aggravation of T2DM. Plasma adiponectin concentrations decreased significantly in obese IRS-2 deficient mice fed on high-fat diet, and decreased adiponectin concentrations might worsen T2DM to severe diabetic condition.

4. Fulminant type 1 diabetes mellitus (FT1DM) in IRS-2 deficient mice

4.1 Onset of FT1DM in IRS-2 deficient mice

Two of eight male IRS-2 deficient mice each at 14 and 24 weeks of age suddenly showed extreme hyperglycemia associated with markedly diminished pancreatic islet size. These extremely hyperglycemic mice had greatly diminished activities of hepatic ACL, FAS, and ME. In these mice, plasma ALT activities were elevated and histochemical analysis of the liver confirmed inflammation. These cases of extreme diabetes resemble the human nonautoimmune FT1DM (Hashimoto et al., 2006). Occurrence rate of FT1D appears to be ~20% in male IRS-2 deficient mice after the age of 8 weeks, and is not observed in the female mice. FT1DM mice showed clinical characteristics of (1) remarkably abrupt onset of disease; (2) very short (< 1 week) duration of diabetic symptoms; (3) acidosis at diagnosis; (4) negative status of islet-related antibodies, ICA, GADAb, IAA or IA-2; (5) virtually no C-peptide secretion; and (6) elevated serum pancreatic enzyme level.

4.2 Characteristics of plasma metabolite and hormones in IRS-2 deficient mice with FT1DM

Because over 50% of male IRS-2 deficient mice after 10 weeks of age tended to show glycosuria with obesity, male IRS-2 deficient mice (8 weeks old) without glycosuria according to Diasticks (Bayer Medical Ltd., Tokyo, Japan) were used as the control. Eight IRS-2 deficient mice (8-20 weeks old) with abrupt increase of blood glucose concentrations over 450 mg/dl (25 mmol/l) within a week and ketonuria with ketosticks (Bayer Medical Ltd.) were determined as FT1DM. Plasma glucose, FFA, TG, TC, insulin and C-peptide concentrations and hepatic enzyme activities were compared between control and diabetic mice. The body weights of the diabetic mice were 26.0 ± 4.6 g (mean ± SD), smaller than those of the control mice (29.6 ± 3.8 g). As the diabetic mice (8-24 weeks old) were older than the control mice (8 weeks old), the reduction of

body weights in the diabetic mice was significant. All the diabetic mice showed ketonuria. In the diabetic mice, the plasma glucose and TC concentrations were significantly higher than those in the controls, whereas plasma insulin and C-peptide concentrations decreased significantly under one third of the control values. There were no significant differences in FFA and TG concentrations between the diabetic and control mice (Table 2).

4.3 Activities of hepatic enzymes related to glucose and lipid metabolism

Activities of HK and GK as rate-limiting enzymes in glycolysis, G6PD as rate-limiting in pentose-phosphate pathway, LDH as cytosol marker enzyme, MDH and AST as crucial enzymes in the malate-aspartate shuttle, PEPCK and FBPase as rate-limiting enzymes in gluconeogenesis, ACL, ME and FAS as rate-limiting enzymes in fatty acid synthesis, PC as oxaloacetate-supplying enzyme to the tricarboxylic acid (TCA) cycle, GLDH as mitochondrial marker enzyme and 3HBD as rate-limiting enzyme in ketone body synthesis were measured. Removed pancreas from the control and the diabetic mice (12 weeks old, plasma glucose 560 mg/dl, plasma insulin <0.2 ng/ml) were examined histopathologically. Existence of the islet-related antibodies was investigated immunohistochemically in sera of NOD mice as autoimmune type 1 diabetic model and IRS2-deficient mice using pancreatic sections prepared from mice before (control mice) and after (diabetic mice) onset of FT1DM.
Activities of HK and GK in glycolysis and MDH in the malate-aspartate shuttle in cytosolic fraction of liver in the diabetic mice were significantly lower than those of the control mice. Activities of FBPase in gluconeogenesis and ME in fatty acid synthesis in liver of the diabetic mice were significantly higher than those of the controls. In the mitochondrial fraction of liver of the diabetic mice, activities of 3-HBD were significantly higher than the controls, whereas activities of AST and PC were significantly lower than those of the controls. In the liver of the diabetic mice, activities of cytosolic LDH, G6PD, AST and mitochondrial GLDH were lower than those of the control mice. The clinical symptoms of FT1DM observed in male IRS-2 deficient mice are significant increase in plasma glucose and cholesterol concentrations and a significant decrease in plasma insulin and C-peptide concentrations. All diabetic mice showed reduction of body weight, glycosuria and ketonuria and they were considered to fall into complete insulin deficiency. In the diabetic mice with insulin deficiency, their plasma TG and FFA concentrations were expected to increase generally, however those concentrations were not changed in IRS-2 deficient diabetic mice. In our previous report (Hashimoto et al., 2006), plasma TG and FFA concentrations decreased significantly notwithstanding plasma glucose and cholesterol concentrations increased significantly in the diabetic IRS-2 deficient mice at 14 weeks old. Liver-specific insulin receptor knockout (LIR-KO) mice with remarkable insulin resistance showed a significant decrease in their plasma TG and FFA concentrations. As IRS-2 deficient mice seemed to have unique regulation mechanism of plasma TG and FFA concentrations, their characteristics in lipid metabolism should be further studied in more IRS-2 deficient mice.
In livers of the diabetic IRS-2 deficient mice, activities of enzymes in glycolysis and the malate-aspartate shuttle were significantly decreased, whereas those in gluconeogenesis and ketone body synthesis were significantly elevated. Decreased activities of pyruvate carboxylase, supplying oxaloacetate to the TCA cycle, suggested depression of citrate synthesis, the rate limiting reaction of TCA cycle, and activation of ketone body synthesis. Moreover, depression in the malate-aspartate shuttle means decreased ATP production. Decrease in glycolysis or increase in gluconeogenesis and ketone body synthesis may be

typical metabolic changes induced by complete insulin deficiency. Decreased activities of LDH, MDH, AST and GLDH in the diabetic IRS-2 deficient mice reflected depression of liver function frequently observed in the diabetic animals.

			Control (n=8)	Diabetic (n=8)
Plasma	Glucose (mg/dl)		223 (20)	569 (77)*
	Free fatty acid (mEq/l)		0.60 (0.02)	1.20 (0.30)*
	Triglyceride (mg/dl)		79.7 (8.9)	97.5 (17.7)
	Total cholesterol (mg/dl)		88.9 (7.7)	162.3 (27.1)*
	Insulin (ng/ml)		1.32 (0.16)	0.28 (0.05)*
	C-peptide (ng/ml)		3.4 (0.4)	1.1 (0.3)*
Liver	Cytosol	HK	6.9 (0.5)	4.7 (0.4)*
		GK	4.2 (0.6)	1.3 (0.3)*
		G6PD	5.1 (0.5)	4.6 (0.3)
		LDH	1294 (86)	1108 (163)
		MDH	4288 (160)	3499 (250)*
		AST	653 (75)	615 (40)
		PEPCK	26 (3)	31 (3)
		FBPase	68 (8)	101 (6)*
		ACL	3.5 (0.4)	3.5 (0.3)
		FAS	4.7 (0.5)	4.9 (0.8)
		ME	17 (2)	30 (2)*
	Mitochondria	GLDH	1834 (116)	1635 (124)
		MDH	2480 (101)	2524 (334)
		AST	1684 (62)	1354 (52)*
		3-HBD	4.1 (0.2)	8.6 (1.4)*
		PC	153 (8)	66 (6)*

Data are presented as mean (SE).
Control means 8-week-old male IRS-2 deficient mice without glycosuria according to Diasticks.
*$p<0.05$ vs. controls
Hepatic enzyme activities are presented as nmol/min/mg protein.
FBPase, fructose-1,6-bisphophatase; 3-HBD, 3-hydroxybutyrate dehydrogenase; PC, pyruvate carboxylase

Table 2. Plasma metabolite concentrations and hepatic enzyme activities in control and diabetic IRS-2 deficient mice

4.4 Pathology and islet antibodies in IRS-2 deficient mice with FT1DM

On histopathological examination, the pancreatic islets of the diabetic mice were significantly decreased in size and number compared to those of the control mice. In particular, size and number of insulin secreted β cells in the diabetic mice decreased significantly compared to those in the controls, whereas number of glucagon secreted α cells decreased a little. Remarkable insulitis by autoimmunity was not observed in pancreatic sections in the diabetic mice (Figure 3). In the sera of the diabetic NOD mice, the islet-related antibodies reacted with their own islets (Figure 4, B1) and IRS2-deficient mouse islets before (Figure 4, B2) and after (Figure 4, B3) onset of FT1DM. In the serum of the control NOD mouse without glycosuria, the islet-related antibodies were not observed (Figure 4, A1-3). In

sera of control and diabetic IRS2-deficient mice, the islet-related antibodies were not observed (Figure 4, C1-3 and D1-3). We also noted observed fatty degeneration in the liver of FT1DM mice. The cause of this degeneration might be increased adiposity due to increased activities of lipogenic enzymes (such as ACL, FAS, and ME) before the change of glucose tolerance in IRS-2 deficient mice. We consider that macrophages noted on histopathologic examination likely appeared to phagocytize the degraded collagen fibrinoid induced by fatty degeneration.

In the diabetic IRS-2 deficient mice, hepatic steatosis is frequently observed. The finding of severe, selective destruction of pancreatic β cells was considered to be one of the characteristics in FT1DM in IRS-2 deficient mice. The diabetic IRS-2 deficient mice did not show the islet-related antibodies observed in the diabetic NOD mice as autoimmune T1DM model. The destruction mechanism of pancreatic islet cells in IRS-2 deficient mice may differ clearly from that in the diabetic NOD mice. IRS-2 deficient mice develop diabetes because of insulin resistance in the liver and failure to undergo β cells hyperplasia. Progress of changes in islet mass should be further studied to investigate pancreatic β cells destruction. At the moment abrupt increase in plasma concentrations and appearance of ketonuria are available indicators to decide complete insulin deficiency caused by pancreatic β cells destruction in diabetic mice. In IRS-2 deficient mice, the sterol regulatory element binding protein (SREBP)-1 downstream genes, such as ATP citrate lyase and fatty acid synthase genes, are significantly increased and an excess amount of lipid is accumulated in their tissues. Accumulated lipid is also considered to be one of the causes of injury to their pancreatic islets. As FT1DM in IRS-2 deficient resembles human FT1DM, IRS-2 deficient mice are a good animal model for T2DM of human and some IRS-2 deficient mice with FT1DM may be a useful animal model for studying the destruction mechanism of pancreatic β cells in progressing to FT1DM.

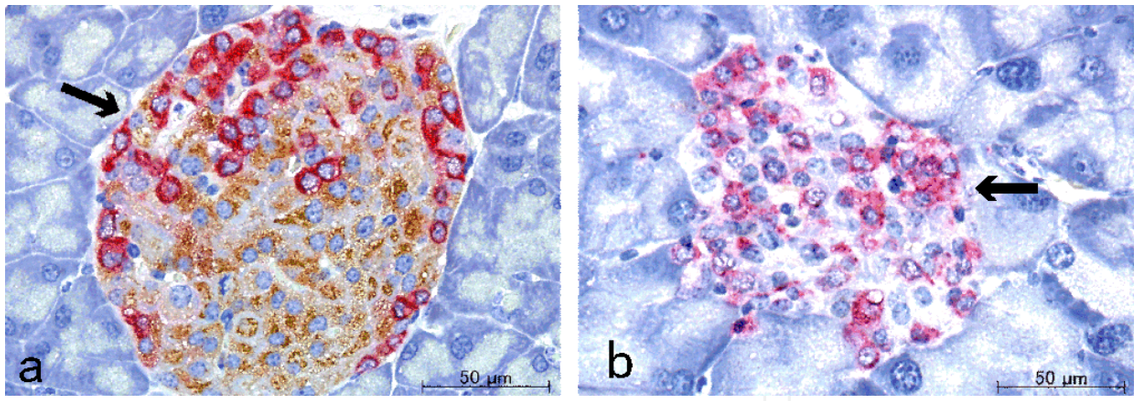


Fig. 3. Histopathological examinations of pancreatic islet cells of IRS-2 deficient mice. Pancreatic islets (arrowheads) in a control mouse (a) and a diabetic mouse (b). Pancreas sections were pretreated with 0.03% H_2O_2 in methanol to block endogenous peroxidase activity, and incubated for 60 min at room temperature with guinea pig anti-swine insulin (Dako Cytomation), followed by 30 min incubation with peroxidase-conjugate rabbit anti-guinea pig immunoglobulin. Then, the sections were incubated for 60 min at room temperature with rabbit anti-human glucagon (Dako Cytomation), followed by 30 min incubation with alkaline phosphatase-labelled polymer conjugated goat anti-rabbit antibody (Nichirei). For double staining, peroxidase (brown, DAB) and alkaline phosphatase (red, New Fuchsin) were used, respectively. Magnification, x 200

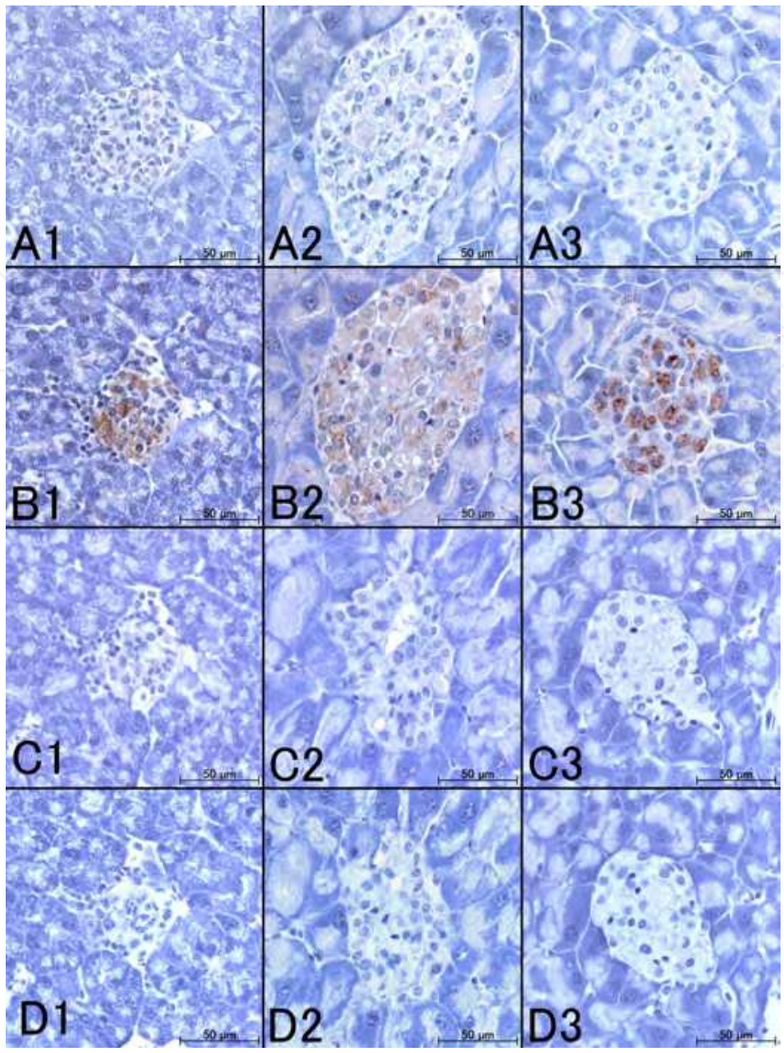


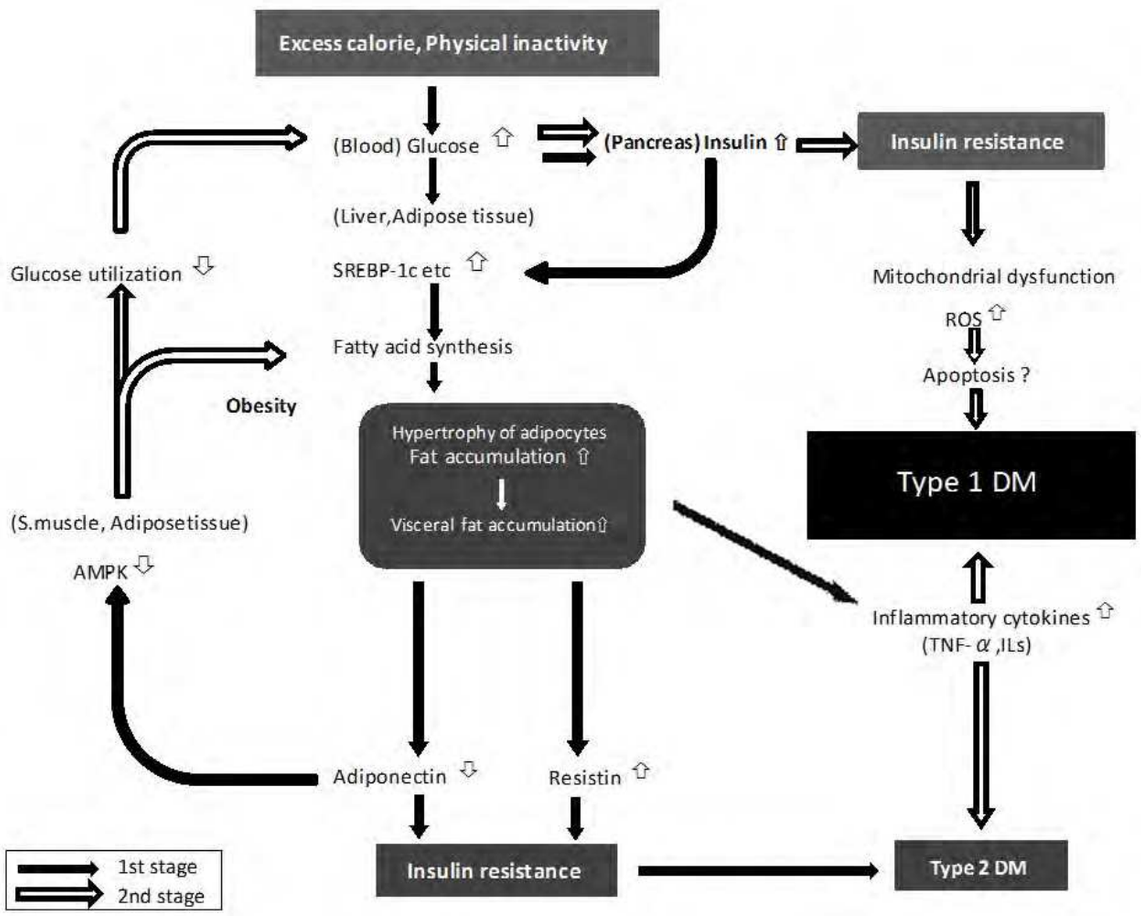
Fig. 4. Observation of islet-associated autoantibodies in serum of NOD and IRS-2 deficient mice. All pancreas specimens were fixed in 10% buffered formalin and embedded paraffin, mounted on amino-silane coated glass slide and stained using the indirect immunoperoxidase method. For each mouse, sera were treated with 0.03% H_2O_2 in methanol to measure the endogenous peroxidase activity. After pre-incubation with the 10% normal rabbit serum (Dako Cytomation) for 10 min at room temperature, sections were then incubated with preclinical NOD/shi mice sera, diabetic NOD/shi mice sera, control IRS-2 mice sera and diabetic IRS-2 mice sera, followed by incubation overnight at 4℃. Sections were serially incubated with polyclonal rabbit anti-mouse IgG/HRP antibodies (Dako Cytomation) for 60 min at room temperature. The peroxidase activity was visualized by incubation in a 0.05M Tris-HCl buffer (pH 7.6) containing 0.02% 3,3'-diaminobenzidine (DAB) and 0.006% H_2O_2 solution for 5 min. Immunostained sections were counterstained with hematoxylin for visualization of nuclei. Column 1, 2 and 3 present diabetic NOD, control IRS-2 deficient and diabetic IRS-2 deficient mouse pancreatic sections, respectively. Control NOD mouse serum (A) reacted with diabetic NOD (A1), control IRS-2 deficient (A2) and diabetic IRS-2 deficient mouse (A3) pancreatic sections. Diabetic NOD (B1-3), control IRS-2 (C1-3) and diabetic IRS-2 (D1-3) mouse sera reacted with pancreatic sections, respectively.

5. Onset mechanism of obesity and diabetes in IRS-2 deficient mice

5.1 Onset mechanism of FT1DM in IRS-2 deficient mice

Figure 5 summarizes onset mechanism of obesity and diabetes in IRS-2 deficient mice. IRS-2 deficient mice tend to fall in insulin resistance. Excess calorie and physical inactivity induce hyperglycemia followed by increased insulin secretion, which accelerates fatty acid synthesis via activation of transcriptional factor, SREBP-1c etc. Acceleration of fatty acid synthesis induces heterotopic accumulation of lipid, and visceral fat accumulation is increased. This situation is defined as obesity. Adiponectin exerts antidiabetic effects on muscles and the liver through AMP-activated protein kinase (AMPK) activation (Yamauchi et al., 2002) and antiatherosclerotic effects by inhibiting monocyte adhesion to endotherial cells and lipid accumulation into macrophages (Ouchi et al., 2001). Thus adiponectin increases glucose uptake and fatty acid oxidation in muscles via the type 1 adiponectin receptor (Yamauchi et al., 2003), and hepatic gluconeogensis via type 2 adiponectin receptor. Moreover adiponectin protects against oxidative stress in skeletal muscle by activating nuclear factor (NF)-κB target genes, manganese superoxide dismutase and inducible nitric oxide synthase (Ikegami et al., 2009). Decreased adiponectin secretion and increased inflammatory cytokines secretion from swelling adipose tissue deteriorate insulin resistance in obese animals (1st stage). Decreased adiponectin causes depression of activity of AMPK which increases glucose utilization and fatty acid β-oxidation in skeletal muscle and adipose tissues (Whitehead et al., 2006). Then hyperglycemia, hyperinsulinemia and accelerated lipid synthesis are maintained and hyper-secretion of insulin force excessively heavy work on pancreatic β cells. In over functional pancreatic islets, β-oxidation of fatty acid is accelerated resulting in excess amount of reactive oxygen species (ROS) production, which induces ROS stress leading to mitochondrial dysfunction and apoptosis of β-cells with low scavenging activity of ROS (2nd stage). It has been reported that adiponectin inhibits fatty acid-induced apoptosis by suppression of ROS generation via both the cAMP/PKA and AMPK pathway in endothelial cells (Kim et al, 2010). Macrophages (but not T cells) infiltration is observed frequently in FT1DM (Shibasaki et al., 2010). In IRS-2 deficient mice with FT1DM macrophage infiltration induced by MCP-1 was observed. Infiltrated macrophages may participate in destruction process of pancreatic islets leading to T1DM. The β cell deficit is believed to be due to autoimmune induced β cell apoptosis mediated by the release of inflammatory cytokines, such as IL-1β and TNF-α, from T lymphocytes and macrophages (Donath et al., 2003). Cytokine-induced β cell death preferentially affects newly forming beta cells, which implies that replicating beta cells might be more vulnerable to cytokine destruction. Efforts to expand beta cell mass in type 1 diabetes by fostering β cell replication are likely to fail unless cytokine-induced apoptosis is concurrently suppressed (Meier et al., 2006). Inflammatory cytokines from corpulent adipocytes appear to participate in destruction of islets β cells leading to T1DM. In autoimmune T1DM, β cells are assumed to be destroyed through a long-standing autoimmune process, whereas in FT1DM, β cells seem to be destroyed very rapidly, probably by a destructive process triggered by viral infection (Hanafusa & Imagawa, 2008). Since IRS-2 deficient mice were maintained under specific pathogen free conditions (Hashimoto et al., 2006), viral infection was deleted from the causes of β cell destruction. Adipocyte-secreted factors associate the pancreatic β cells destructions. Chronic exposure of human islets to leptin leads to β cell apoptosis (Donath et al., 2003). TNFα, in combination with other cytokines, accelerates dysfunction and destruction of the β cell (Eizirik & Mandrup-Poulsen, 2001). IL-6 released by adipocytes may be responsible for the increases in plasma IL-6 concentrations observed in obesity and

at least in combination with other cytokines, IL-6 has cytotoxic effects on β cell (Eizirik et al., 1994). Increased FFA levels are known to be toxic for β cell, leading to the concept of lipotoxicity (McGarry & Dobbins, 1999). The toxic effect of FFA is mediated via formation of ceramide, increased nitric oxide production and activation of the apoptotic mitochondrial pathway (Maedler et al., 2001). Elevated glucose concentrations induced β cell apoptosis at higher concentration in rodent islet (Efanova et al., 1998). In human islets glucose-induced β cell apoptosis and dysfunction are mediated by β cell production and secretion of IL-1β. Chronic hyperglycemia increases production of ROS, which may cause oxidative damage in β cell (Matsuoka et al., 1997; Laybutt et al., 2002). IL-1β and ROS activate the transcription factor nuclear transcription factor (NF) κB, which plays a critical role in mediating inflammatory responses. A series of inflammatory reaction appear to have important roles in the β cell destruction process in IRS-2 deficient mice with insulin resistance.



SREBP, sterol regulatory element binding protein; AMPK, AMP-activated protein kinase; ROS, reactive oxygen species;
TNF, tumor necrosis factor; IL, interleukins

Fig. 5. Onset mechanism of obesity and diabetes in IRS-2 deficient mice

5.2 Comparison of pathology of FT1DM between IRS-2 deficient mice and human patients

IRS-2 deficient mice with FT1DM show remarkable body weight loss, polydipsia, polyuria, glycosuria and ketonuria as typical symptoms of T1DM as reported in human FT1DM patients. Laboratory data in IRS-2 deficient mice with FT1DM reveal hyperglycemia, hyperlipidemia and remarkable decrease in insulin secretion as in human FT1DM patients (Table 3). The above symptoms of T1DM were onset abruptly after hyperglycemia was observed in IRS-2 deficient mice. Insulitis with macrophage dominant infiltration was observed in IRS-2 deficient mice and human FT1DM. Destruction mechanism of β cells associated HLA, viral infection and pregnancy were investigated in detail in human FT1DM patients (Kawabata et al., 2009; Murabayashi et al., 2009; Tan & Loh, 2010), whereas association with MHC was not investigated in IRS-2 deficient mice. Since FT1DM was observed in only male IRS-2 deficient mice, pregnancy is not associated with onset of FT1DM. Inflammatory cytokines play a major role in destruction process of pancreatic β cell in both IRS-2 mice and human FT1DM patients. Trigger of the β cell destruction process is different between IRS-2 mice and human. Insulin resistance by increase in inflammatory cytokines seemed to be main cause to lead β cell destruction in IRS-2 deficient mice, whereas viral infection may be a trigger for destruction mechanism in human FT1DM patients.

	IRS-2 deficient mice	Human patients	References
Clinical characteristics			
Body weight loss	Remarkable	Remarkable	Imagawa et al. (2003)
Polydipsia	Positive	Positive	Imagawa et al. (2003)
Polyuria	Positive	Positive	Imagawa et al. (2003)
Glycosuria	Positive	Positive	Imagawa et al. (2003)
Ketonuria	Positive	Positive	Imagawa et al. (2003)
Laboratory data			
Fasting plasma glucose (mg/dl)	570 (480 – 640)	711 (300 – 1293)	Shimizu et a. (2006)
Fasting plasma C peptide (ng/ml)	1.1 ± 0.3*	< 0.5	Shibasaki et al. (2010)
Serum triglyceride (mmol/l)	1.1 ± 0.2*	2.0 ± 1.8**	Imagawa et al. (2003)
Serum total cholesterol (mmol/l)	4.2 ± 0.7*	5.1 ± 1.6**	Imagawa et al. (2003)
Insulitis	Macrophages dominant infiltration	Macrophages as the main cell type in insulitis lesion, followed by T lymphocytes	Hanafusa & Imagawa (2008)
Islet related autoantibodies	Negative	Negative	Imagawa et al. (2003)

*Mean ± SE, **Mean ± SD

Table 3. Characteristics of FT1D in IRS-2 deficient mice and human patients

Type 1 diabetes is a polygenic disease. Approximately 50% of the genetic susceptibility can be explained by allele in HLA class II region, in particular certain DQ alleles. More than 95%

of type 1 diabetic patients carry these predisposing alleles, but the occurrence of these alleles in the background population is high, approximately 50%. It is believed that the diabetes predisposing DQ antigens have a shape of the antigen presenting groove of the molecule that leads to more efficient presentation of β cell associated autoantigens (Donath et al., 2003). HLA comment should be in the text. In FT1DM patients, the haplotype frequency of HLA DRB1*0901-DQB1*0303 was significantly higher than those in controls (Moreau et al., 2008). HLA phenotyping of these Caucasian patients did not find the specific HLA haplotype (DRB1*0405-DQB1*0401) found to be linked to FT1D in Japanese patients. More investigation about haplotype frequency of MHC was necessary for IRS-2 mice in the destruction process of pancreatic β cells.

6. Conclusion

IRS-2 mice tend to become obese accompanying insulin resistance after 8 weeks of age. IRS-2 deficient mice develop diabetes, presumably due to inadequate β cell proliferation combined with insulin resistance compared to IRS-1 deficient mice with the β cell hyperplasia to compensate for the insulin resistance. Heterotopic accumulation of lipid observed frequently in obese IRS-2 mice, and corpulent adipocytes secrete various inflammatory cytokines, such as TNF-α and ILs, whereas production of adiponectin as antidiabetic agent is decreased significantly. About 20% of male IRS-2 deficient mice showed clinical characteristics of (1) remarkably abrupt onset of disease; (2) very short (< 1 week) duration of diabetic symptoms; (3) acidosis at diagnosis; (4) negative status of islet-related antibodies; (5) virtually no C-peptide secretion; and (6) elevated serum pancreatic enzyme level. These symptoms resembled the features of human nonautoimmune FT1DM. In IRS-2 deficient mice with FT1DM, insulitis with macrophage dominated infiltration to islet β cell area was observed frequently as in human FT1DM patients. Inflammatory cytokines appear to have important roles in the process of β cell destruction leading to FT1DM. IRS-2 deficient mice are considered to be useful animal model for studying the mechanism of β cell destruction leading to FT1DM.

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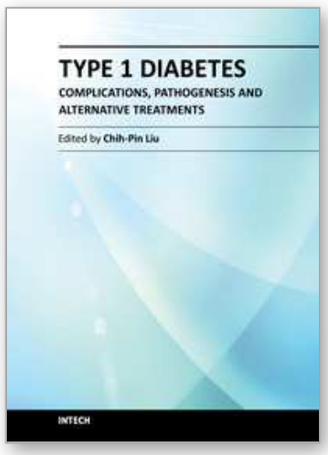

Type 1 Diabetes - Complications, Pathogenesis, and Alternative Treatments

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This book is intended as an overview of recent progress in type 1 diabetes research worldwide, with a focus on different research areas relevant to this disease. These include: diabetes mellitus and complications, psychological aspects of diabetes, perspectives of diabetes pathogenesis, identification and monitoring of diabetes mellitus, and alternative treatments for diabetes. In preparing this book, leading investigators from several countries in these five different categories were invited to contribute a chapter to this book. We have striven for a coherent presentation of concepts based on experiments and observation from the authors own research and from existing published reports. Therefore, the materials presented in this book are expected to be up to date in each research area. While there is no doubt that this book may have omitted some important findings in diabetes field, we hope the information included in this book will be useful for both basic science and clinical investigators. We also hope that diabetes patients and their family will benefit from reading the chapters in this book.

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